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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,126	09/27/2000	Gunther Hartmann	C1039/7044 (AWS)	6887

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/672,126	Applicant(s) HARTMANN ET AL.	
	Examiner Quang Nguyen, Ph.D.	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003 and 02 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,47,65,82,103,122,143,159,176,199 and 201-203* is/are pending in the application.

4a) Of the above claim(s) *47,122,143,159 and 201* is/are withdrawn from consideration.

5)☒ Claim(s) *202 and 203* is/are allowed.

6)☒ Claim(s) *1-18,20-24,65,82,103,176 and 199* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendments filed on 2/20/03 and 6/2/03 in Paper Nos. 13 and 16, respectively have been entered.

Claims 1-24, 47, 65, 82, 103, 122, 143, 159, 176, 199 and 201-203 are pending in the present application.

Claims 47, 122, 143, 159 and 201 have been withdrawn from further consideration because they are drawn to non-elected inventions.

Accordingly, amended claims 1-24, 65, 82, 103, 176, 199 and 202-203 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Objections

Claim 1 is objected to because the phrase "comprising co-administering an effective amount ..." is not grammatically correct. Co-administering into what? The insertion of the phrase - - into the subject - - after the term "co-administering" would obviate this objection. Appropriate correction is required.

Response to Amendment

The rejection for the lack of Written Description is withdrawn in light of Applicants' amendment.

Upon reconsideration, following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Amended claims 1-18, 20-24, 65, 82, 103, 176 and 199 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A. A method which calls for administration of IFN-α to a mammal, the improvement comprising co-administering to said mammal an effective amount of an isolated immunostimulatory nucleic acid, wherein said isolated nucleic acid comprises a poly-G sequence at each end and a central palindromic sequence comprising an unmethylated CpG dinucleotide; and

B. Methods for supplementing IFN-α treatment of a mammal, for increasing efficacy of IFN-α treatment of a mammal, for decreasing a dose of IFN-α effective for treating a mammal, for reducing an IFN-α treatment-related side effect in a mammal receiving or in need of treatment with IFN-α, for stimulating production of a plurality of type I interferon (IFN) subtypes, for inhibiting IL-12 production using the same isolated immunostimulatory nucleic acid in A;

does not reasonably provide enablement for the methods as claimed in any subject and co-administration of an isolated immunostimulatory nucleic acid comprising a poly-G sequence at each end and a central palindromic sequence comprising an unmethylated CpG dinucleotide wherein the immunostimulatory nucleic acid is 8 or 9 nucleotides long. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for the present broadly claimed invention for the reasons discussed below.

(a) The breadth of the claims. The claims encompass improved methods that call for administration of IFN-α to any subject including any vertebrate such as a fish, a frog as well as a mammal (see instant specification, page 30, lines 10-8), wherein the improvement comprising co-administering into the subject an effective amount of an isolated immunostimulatory nucleic acid, wherein said isolated nucleic acid is at least 8 nucleotides long (including 8 or 9 nucleotides long) and comprises a poly-G-sequence at each end and a central palindromic sequence comprising an ummethylated CpG dinucleotides. The claims are also drawn to a method for stimulating production of a plurality of type I interferon subtypes or for inhibiting IL-12 producing comprising contacting type I interferon producing cells or IL-12 producing cells in the presence of interferon-producing cells, respectively, using an effective amount of the same isolated immunostimulatory nucleic acid.

(b) The state and th unpredictability of the prior art. At the effective filing date of the present application, little was known on the immune responses in vertebrate species such as a fish or a frog, let alone on the specific induction of type I interferon (e.g., IFN-α/β) to any significant level by the immunostimulatory nucleic acids of the present invention to yield the desired results contemplated by Applicants (e.g., increasing efficacy of IFN-α treatment, decreasing a dose of IFN-α effective for treatment, reducing an IFN-α treatment related side effects). Additionally, there is no evidence of record indicating or suggesting the presence of a cell population functionally equivalent to the human immature plasmacytoid dendritic cells (PDC), the major IFN-α producing cell being activated by the immunostimulatory nucleic acid of the present invention, in species such as fish or frog or numerous other non-mammalian vertebrate species. Nor is there any evidence for the existence of a cell population functionally equivalent to the human γδ T cells in such non-mammalian vertebrate species, being activated indirectly by the immunostimulatory nucleic acid of the present invention to yield the desired results contemplated by Applicants. Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03).

(c) The amount of direction or guidance presented. As written the methods as claimed utilize an isolated immunostimulatory nucleic acid at least 8 nucleotides long and comprising a poly-G sequence at each end and a central palindormic sequence comprising an unmethylated CpG dinucleotide. However, as defined by the present application a poly-G sequence refers to at least 3 Gs in a row (page 26, line 10), then how can an immunostimulatory nucleic acid with 8 or 9 nucleotides in length contain all

the recited limitations (e.g., a poly-G sequence at each end and a CpG dinucleotide in a palindromic sequence). The exemplification showed that only certain CpG oligonucleotides such as ODN 1585 (ggGGTCAACGTTGAgggggG, SEQ ID NO:1), ODN 2216 (ggGGGACGATCGTCgggggG, SEQ ID NO:7), all of which contain at least one CG dinucleotide in a palindromic sequence and a poly-G sequence at each end, are capable of inducing plasmacytoid dendritic cells (pDC), the **principle type I interferon producing cells** in human blood and a critical effector cell type of the immune system for antiviral and antitumor responses (Siegal et al., Science 284:1835-1837, 1999, IDS), to produce IFN-α, and not other CpG containing oligonucleotides such as ODN 2006 (tctcgttttgtcgttttgtcgtt, SEQ ID NO:147, see examples 5-6). It is further noted that control oligonucleotides for ODN 2216 such as ODN 2197 (7-deaza-guanosine substations in poly G ends, unable to form G tetrads) and ODN 2198 (CG and poly-G ends but no palindrome) do not induce any significant amount of IFN-α in PBMC; nor do poly (I:C) molecule (see example 5). Additionally, the specification discloses that ODN 1585 (ggGGTCAACGTTGAgggggG, SEQ ID NO: 1) can inhibit the production of IL-12 whereas ODN 2006 (tctcgttttgtcgttttgtcgtt, SEQ ID NO:147, containing CG dinucleotides without a palindrome nor poly-G ends) do not inhibit the production of IL-12 (see example 13). Given the guidance and examples provided by the instant specification, and in light of the general state of the art as discussed above, it would have required undue experimentation for a skilled artisan to make and use the methods as broadly claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 8, it is unclear what is encompassed by the phrase "wherein the immunostimulatory nucleic acid is modified". How is the nucleic acid modified? Which components of the nucleic acid being modified? The metes and bounds of the claim are not clearly determined.

In claim 11, the phrase "wherein the immunostimulatory nucleic acid is not a palindrome" is unclear. It is noted that the immunostimulatory nucleic acid contains a

central palindromic sequence comprising an unmethylated CpG dinucleotide in claim 1 from which claim 11 is dependent upon. Clarification is requested because the metes and bounds of the claim are not clearly determined.

In claim 12, it is unclear what is encompassed by the phrase "wherein the immunostimulatory nucleic acid is a CpG nucleic acid". What do Applicants intend to mean a CpG nucleic acid. Any nucleic acid containing a CpG dinucleotide is a CpG nucleic acid? It is noted that the imunostimulatory nucleic acid of claim 1 already contains a CpG dinucleotide. Clarification is requested because the metes and bounds of the claim are not clearly determined.

In claim 13 and its dependent claims, the phrase "wherein the immunostimulatory nucleic acid is a non-CpG nucleic acid" is unclear. It is noted that the immunostimulatory nucleic acid of claim 1 from which claim 13 is dependent upon, must contain a CpG dinucleotide. Therefore, it is unclear what do Applicants intend to claim.

In claim 16, the phrase "wherein the immunostimulatory is any combination of at least two nucleic acids selected from the group consisting of: CpG nucleic acids, T-rich nucleic acids, and poly-G nucleic acids" is unclear. How can the immunostimulatory nucleic acid of claim 1 from which claim 16 is dependent upon is a combination of CpG nucleic acids and T-rich nucleic acids? Or T-rich nucleic acids and poly-G nucleic acids? Clarification is requested because the metes and bounds of the claim are not clearly determined.

Conclusions

Claims 202 and 203 are allowable.

Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

PATENT EXAMINER